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PATENT APPLICATION
Docket No. 16778.5a.1.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of		)
	Ole Thastrup et al.	)
Serial No.:	10/072,036	)
Confirmation No.:	3012	) Group Art Unit 1633
Filed:	February 5, 2002	)
For:	A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE	)
Examiner:	Michael D. Burkhart	)
Customer No.:	022913	)

BRIEF OF APPELLANT

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PO Box 1450
Alexandria, VA 22313-1450

This is an appeal to the Board of Patent Appeals and Interferences (the "Board") from the Final Office Action mailed February 19, 2009 (the "Final Office Action") wherein the Examiner rejected claims 44-54, 73-80 and 82. The Notice of Appeal was filed on May 4, 2009, and a petition for an extension of time is being filed herewith. This Brief is being filed pursuant to the provisions of 37 C.F.R. § 41.37. This Brief is accompanied by the requisite fee of $540.00, as provided by 37 C.F.R. § 41.20(b)(2). The Commissioner is hereby authorized to charge any additional fees associated with this communication, or to credit any overpayment, to Deposit Account No. 23-3178.

I. REAL PARTY IN INTEREST

The real party at interest is Thermo Fisher Scientific, which wholly owns Fisher BioImage APS as a subsidiary. Fisher BioImage APS is the assignee by way of assignment from BioImage A/S (the corresponding assignment document was recorded in the United States Patent and Trademark Office at Reel/Frame 018120/0677 on August 17, 2006), by way of assignment from Novo Nordisk A/S (the corresponding assignment document was recorded in the United States Patent and Trademark Office at Reel/Frame 018128/0079 on August 17, 2006), by way of assignment from the named inventors, Ole Thastrup, Sara Petersen Bjorn, Soren Tullin, Kasper Almholt, and Kurt Scudder, the corresponding assignment document was recorded in the United States Patent and Trademark Office at Reel/Frame 018127/0767 on August 17, 2006).

II. RELATED APPEALS AND INTERFERENCES

A Notice of Appeal was previously filed in the instant application on August 29, 2007 to appeal from a Final Office Action that rejected all of the pending claims in view of the Carey reference.[1] However, that appeal was never docketed with the Board. The Notice of Appeal was accompanied by a Pre-Appeal Brief Conference Request, and the Pre-Appeal Brief Conference decision dated October 12, 2007 withdrew the rejections under the Carey reference and reopened prosecution. A copy of the Pre-Appeal Brief Conference Decision is included in the Related Proceedings Appendix.

[1] Evidence Using A Green Fluorescent Protein-Glucocorticoid Receptor Chimera that the RAN/TC4 GTPase Mediates An Essential Function Independent Of Nuclear Protein Import, KL Carey et al., *The Journal of Cell Biology*, Vol. 133, No. 5, June 1996, pp. 985-996 (hereinafter, "Carey")

III. STATUS OF CLAIMS

Claims 1-43 were originally filed in the application. Claims 44-82 were added by amendment, Claims 1-43 and 55-72 have been canceled and claim 81 was withdrawn from consideration as being a nonelected species. Claims 44-54, 73-80, and 82 remain pending and were finally rejected in the Final Office Action mailed February 19, 2009. Claims 44-54, 73-80, and 82, which are all finally rejected, are being appealed.

IV. STATUS OF AMENDMENTS

The Appellant has not submitted any amendments subsequent to the Final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The Appellant's invention is a method of using a new "hybrid polypeptide" for screening compounds of a compound library to detect new biologically active compounds, which may be useful as new drugs (paragraphs [0001, 0013, and 0027]).[2] In claim 46, the new "hybrid polypeptide" of the present invention includes a "luminophore" portion and a portion that is "a subunit of a biologically active polypeptide affecting intracellular processes, which subunit exhibits a biological activity of the [biologically active] polypeptide." In claims 44 and 45, the new "hybrid polypeptide" includes a "luminophore" portion and a portion that is a "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component." The specification teaches that "a component of an intracellular pathway" is a biologically active polypeptide (paragraph [0060]).

As a background, other types of "hybrid polypeptides" have been described in the Carey reference[3] and the Htun reference[4] (paragraph [0010]). The hybrid polypeptides of Htun and Carey each include a luminophore polypeptide linked to a full, natural protein of interest, not to a subunit of such a protein.

The Carey and Htun references, which have substantially the same teachings as one another, validate that hybrid polypeptides having a luminophore and a full, natural protein of interest translocate similarly to the full, natural protein. Specifically, these references show that a hybrid polypeptide (GR-GFP) with a luminophore (GFP) and a full, natural protein of interest (GR) translocated similar to the natural protein (GR) by using well-known compounds (e.g., dexamethasone, etc.) that had well-established biological activity on the natural GR protein. That is, the well-known compounds with the well-known biological activity of modulating the translocation of the natural GR protein similarly modulated the translocation of the GR-GFP hybrid polypeptide. The hybrid polypeptides of Htun and Carey do not include a "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a

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[2] For convenience, the claimed subject matter is summarized with reference to the pre-grant publication of the application having publication number US 2003/0082564.

[3] Evidence Using A Green Fluorescent Protein-Glucocorticoid Receptor Chimera that the RAN/TC4 GTPase Mediates An Essential Function Independent Of Nuclear Protein Import, KL Carey et al., *The Journal of Cell Biology*, Vol. 133, No. 5, June 1996, pp. 985-996; hereinafter, "Carey."

[4] Visualization Of Glucocorticoid Receptor Translocation And Intranuclear Organization In Living Cells With A Green Fluorescent Protein Chimera, H. Htun et al., *Proc. Natl. Acad. Sci. USA*, Vol. 93, May 1996, pp 4845-4850; hereinafter, "Htun."

biological activity of the component" as required by claims 44-45, nor a "subunit of a biologically active polypeptide affecting intracellular processes, which subunit exhibits a biological activity of the polypeptide" as required by claim 46.

In independent claims 44 and 45, the claimed method is for using the new hybrid polypeptide to screen a library of compounds to detect a compound that has a biological function or biological effect on the subunit of the component of an intracellular pathway, where the subunit "exhibits a biological activity of the component" (paragraphs [0013-0014, 0026-0027, and 0041-0057]). The method involves screening the library of compounds to determine whether the compound has a biological function or biological effect on the subunit (paragraphs [0012-0014, 0026-0027, 0033-0036, 0038-0039, and 0059-0061]). The method determines that a compound has a biological function or biological effect on the subunit by monitoring changes in light emitted from the luminophore portion of the hybrid polypeptide. The changes in light are indicative of the hybrid polypeptide translocating within the cell, and such translocation is indicative that the compound has a biological activity on the component of the intracellular pathway (e.g., the biologically active polypeptide). Accordingly, the hybrid polypeptide can be used in screenings to determine whether or not a compound is biologically active with the subunit and component of the intracellular pathway.

Independent claim 46 is similar to claims 44 and 45 in that the new hybrid polypeptide (having a luminophore and a subunit of a biologically active polypeptide) is used to screen a library of compounds to detect a new compound that has a biological function or biological effect on the subunit. The culturing, incubating, and screening steps are substantially similar to claims 44 and 45. A difference is that the "subunit" in claim 46 is specifically defined to be a "subunit of a biologically active polypeptide affecting intracellular processes, which subunit exhibits a biological activity of the polypeptide" (paragraphs [0041, 0043-0057, and 60-61]). Support in the specification of the elements of claim 46 is substantially identical to the support for claims 44 and 45.

The claims 47-54, 73-80, and 82 depend from one or more of claims 44-46, and define additional aspects of the invention. For example, these dependent claims relate to the following: extraction of quantitative information; measuring light emitted from the hybrid polypeptide; the identity of the compound to be screened; properties of the hybrid polypeptide; the cells being fixed; the cells are stably transformed to produce the hybrid polypeptide; and digital image

manipulation. Support for the dependent claims is found throughout the specification, including the portions of the specification recited to support independent claims 44-46, in the Examples, and in paragraphs [0012-0014, 0029-0039, and 0059-0061].

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Issue 1: Whether claims 44-52, 73, 77-80 and 82 are anticipated under 35 U.S.C. §102(b) by the Htun reference as evidenced by the Carey reference or the Agarwal reference.[5]

Issue 2: Whether claims 44-52, 73-80 and 82 are unpatentable under 35 U.S.C. § 103(a) over the Htun reference as evidenced by the Carey reference in view of the Agarwal reference, Sonenberg (US 5,874,231), and Dunlay (US 5,989,835).

Issue 3: Whether claims 53 and 54 are unpatentable under 35 U.S.C. § 103(a) over the Htun reference, the Carey reference, the Agarwal reference, Sonenberg (US 5,874,231), and Dunlay (US 5,989,835) as applied to claims 44-52, 73-80, and 82 above, and further in view of the Cormack reference.[6]

Issue 4: Whether claim 48 fails to comply with the written description requirement under 35 U.S.C. §112, first paragraph.

[5] The Antiglucocorticoid Action Of Mifepristone, MK Agarwal, *Parmacol. Ther.*, Vol. 70, No. 3, pp. 183-213, 1996; hereinafter, "Agarwal."

[6] FACS-Optimized Mutants of the Green Fluorescent Protein (GFP), BP Cormack et al., *Gene*, vol. 173: pp. 33-38, 1996; hereinafter, "Cormack."

VII. ARGUMENT

A. Issue 1: Whether claims 44-52, 73, 77-80 and 82 are anticipated under 35 U.S.C. §102(b) by the Htun reference as evidenced by the Carey reference or the Agarwal reference.

Claims 44-52, 73, 77-80 and 82 were rejected under 35 U.S.C. § 102(b) as being anticipated by the Htun reference as evidenced by the Carey reference or the Agarwal reference. In order to reject a claim under 35 USC § 102(b) as being anticipated, the Htun reference must teach each and every element of the claim. However, the Examiner has not established that the Htun reference teaches each and every element of the independent claims.

The Htun reference teaches a hybrid polypeptide (GR-GFP) that includes a full, natural glucocorticoid receptor (GR) portion and a green fluorescent protein (GFP) portion, which is encoded by a nucleic acid that is transiently transfected into cells (page 4845, second column). The hybrid polypeptide was tested to determine whether it translocated similarly to the natural GR protein by exposing the hybrid polypeptide to compounds that had well-known and well-established biological activities on the natural GR protein. More specifically, the Htun reference validated that GR-GFP was a hybrid polypeptide that had translocation properties similar to the natural GR protein by studying the translocation of GR-GFP in response to dexamethasone, RU486, progesterone, and 17beta-estradiol, and comparing the translocation activity of the GR-GFP with the well-known activity of these compounds on the natural GR protein (page 4847, second column). The Htun reference also theorized in the last paragraph that GR-GFP was "an invaluable tool for understanding further details of receptor activation, the translocation process, interaction of receptors with components of the eukaryotic interphase nuclei, and mechanisms of transcriptional activation by steroid receptors" (page 4850, first column).

The Examiner alleges that the Carey reference is evidence that the natural GR protein forms a complex with Ran/TC4 GTPase (Ran), and thereby alleges that the natural GR protein is a "subunit" of that "component" (e.g., complex of Ran/GR) (see Office Action mailed 12/31/2007, page 4). The Examiner also alleges the Agarwal reference is evidence that the natural GR protein forms a complex with heat shock proteins (HSP) in the cytoplasm, and asserts that a HSP/GR complex is a "component of an intracellular pathway" and GR is a "subunit" of that "component" (see Office Action mailed 12/31/2007, page 4). There are several problems

with these assertions.

i. The Htun reference, even in view of the Carey and Agarwal references, does not teach a "subunit [that] exhibits a biological activity of the component" as recited in claims 44-45, 47-54, 74-80, and 82.

Claims 44-45 require "detecting intracellular translocation of a subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component." Accordingly, the component must have a biological activity, and the subunit must have the biological activity of the component.

As recited above, the Examiner considered the Ran/GR multi-protein complex to be a "component of an intracellular pathway," and GR to be a "subunit" of that component. There are two problems with this analysis.

First, the Carey reference does not disclose that the natural GR protein binds with Ran to form a complex. The Carey reference provides data and discussions that Ran may be involved in the nuclear import of an activated natural GR protein, but none of the data or discussions states that Ran binds the natural GR protein. In fact, the Carey reference indicates otherwise. The Carey reference states: "the data do not prove that Ran is directly involved in the nuclear transport of GR-GFP" (last paragraph of the second column of page 989). If Ran is not "directly involved in the nuclear transport," it is not forming a complex with the GR protein. Moreover, the Carey reference admits that "it remains possible that the inhibition of GR-GFP import is a secondary consequence of a disruption of the nuclear export machinery" (third paragraph of the first column of page 994). Accordingly, the Carey reference does not establish that Ran binds with the natural GR protein, and thereby, there is no evidence of a Ran/GR multi-protein complex for the natural GR protein to be a subunit of. Additionally, Appellant is not aware of any evidence showing that the natural GR protein binds with Ran to form a Ran/GR complex. Thus, the Examiner has not established that the natural GR protein is a "subunit of a component of an intracellular pathway affecting intracellular processes," as recited in claims 44-45.

Second, assuming, *arguendo*, that the natural GR protein does bind Ran, there is no evidence that the natural GR protein has the biological activity of a Ran/GR complex. For the sake of argument only, a Ran/GR complex would have a biological activity of transport from the cytoplasm into the nucleus. As evidenced by the Carey reference, if the nuclear import protein

machinery is compromised, such as by a mutant Ran, then the natural GR protein cannot enter into the nucleus. Accordingly, the Carey reference demonstrates that the natural GR protein would not have the biological activity of a Ran/GR multi-protein complex if it existed. Therefore, the Examiner has not established that the "subunit exhibits a biological activity of the component" as recited in claims 44-45 because the Examiner has not established that the natural GR protein exhibits the biological activity of a Ran/GR complex.

As recited above, the Examiner has also asserted that the Agarwal references teaches that the natural GR protein inherently binds heat shock proteins (HSP) in the cytoplasm, and asserts that the natural GR protein would allegedly be a subunit of the HSP/GR complex. However, Agarwal does not teach that the natural GR protein "exhibits the biological activity" of the HSP/GR complex, and has not established that the HSP/GR complex translocates as a "component of an intracellular pathway." Appellant is not aware of any evidence that GR "exhibits the biological activity" of the HSP/GR complex or that the HSP/GR complex translocates as part of an intracellular pathway, and thereby, the claim limitations are not satisfied. Therefore, the Htun reference cannot anticipate claims 44-45, 47-54, 74-80, and 82 because the Htun reference, even under the evidence of Carey and/or Agarwal, does not teach a "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component" as recited under the claims.

ii. The Htun reference, even in view of the Carey and Agarwal references, does not teach the "screening" required in claims 44-45, 47-54, 74-80, and 82.

The Htun reference does not teach a hybrid polypeptide that can be used "for screening a library of compounds to detect a biologically active compound" and "screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells." The claim element "screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit" needs to be defined in order to understand the scope of the claim elements,

Earlier in the prosecution history of the instant patent application, the term "screening" was the subject of overly-broad definitions. A declaration by Chris M. Ireland, Ph.D., was filed to identify that "screening" is a term of art, and to define the term with regard to the

understanding of one of ordinary skill in the art. The declaration is reproduced in the Evidence Appendix. In accordance with the declaration, testing compounds with well-known and well-established biological activities relative to the natural GR protein does not constitute "screening" these compounds because the biological activities of those compounds were already well-known and well-established, and thereby those activities could not be "determined" again. The Htun reference used the well-known and well-established biological function and biological effect on the natural GR protein by dexamethasone, RU486, progesterone, and 17beta-estradiol to validate that the GR-GFP hybrid polypeptide translocated similarly to the natural GR protein. By virtue of dexamethasone, RU486, progesterone, and 17beta-estradiol having well-known and well-established biological activities on the natural GR protein, these compounds were not "screened" to "detect a biologically active compound" because the biological activities on GR were already known and detected long ago. If the biological function or biological effect of these compounds on the natural GR protein was not previously known, then these compounds could not have been used to validate that the GR-GFP hybrid polypeptide translocated similarly to the natural GR protein. Thus, testing well-known compounds with well-known biological activities on the natural GR protein does not constitute "screening" to determine "a biological function or biological effect on the subunit" under the presently claimed invention.

The Examiner reasons that determining the effects of dexamethasone, RU486, progesterone, and 17beta-estradiol on the translocation of the GR-GFP hybrid polypeptide from the cytoplasm to the nucleus is a "screening." Applicant respectfully asserts that this reasoning is incorrect because it does not consider the actual claim language. The Appellants do not claim a method of screening for determining effects on a hybrid polypeptide. In fact, the claims recite "screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect *on the subunit*." According to the Examiner's theory, the "subunit" is the GR protein, not the GR-GFP hybrid polypeptide. The fact that compounds of Htun each had a well-known and well-established biological function and biological effects on GR shows that Htun does not teach a "screening" with respect to the "subunit."

The Appellants invented a method of "screening" a library of compounds to determine whether any of the compounds had a biological function or biological effect on the "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a

biological activity of the component." Such a "screening" is not taught in the Htun reference, and therefore the Htun reference cannot anticipate claims 44-45, 47-54, 74-80, and 82.

iii. The Htun reference, even in view of the Carey and Agarwal references, does not teach each and every element in claim 46.

The Examiner also has not established that the Htun reference teaches each and every element of claim 46. For the same reasons that the Htun reference does not meet the "screening" limitations of claims 44 and 45, the Htun reference does not meet those same limitations in claim 46. Additionally, claim 46 requires that the "subunit" is "of a biologically active polypeptide" and that the "subunit exhibits a biological activity of the polypeptide." As such, the "subunit" of claim 46 is not a complete biologically active polypeptide (e.g., not a full, natural protein), but rather is a "subunit" or portion thereof that has the biological activity of the complete biologically active polypeptide. Claim 46 further requires "culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a luminophore linked to the subunit under conditions permitting expression of the nucleotide sequence." The Htun reference does not meet these limitations because as discussed above, there is no evidence that a Ran/GR complex exists or that GR exhibits a "biological activity" of Ran/GR. Claim 46 is also not anticipated for another reason. Even assuming that a Ran/GR complex exists and even assuming that GR "exhibits a biological activity" of Ran/GR, such as Ran/GR complex would not be "a biologically active polypeptide" because it would lack peptide linkages between the Ran and GR proteins. The same can be said of a HSP/GR complex. Since the Examiner has not established that Htun teaches a hybrid polypeptide that includes a "subunit of a biologically active polypeptide," Htun cannot anticipate claim 46.

iv. The Htun reference, even in view of the Carey and Agarwal references, does not teach each and every element in claim 73.

Claim 73 depends from claims 44, 45, and 46, and thereby includes the limitations thereof. As such, the Htun reference does not anticipate claim 73 for the same reasons it does not anticipate any one of claims 44-46. Additionally, claim 73 recites, "the light emitted from the luminophore is obtained by automated image acquisition." The specification teaches that "the recording of spatially distributed luminescence emitted from the luminophore is performed

by an apparatus for measuring the distribution of fluorescence in the cell" and then recites the components of the "apparatus" (paragraph [0033]). The next paragraph ([0034]) teaches that the apparatus system is automated. In contrast, the Htun reference does not teach that the light emitted from the luminophore can be obtained by automated image acquisition. Htun only teaches manipulating manually acquired digital images of the light in a computer. The Examiner alleges that suffices to anticipate claim 73. But this allegation does not consider the actual recited claim limitations. Claim 73 requires that "the light emitted from the luminophore is obtained by automated image acquisition." It is not enough that a digital image of light emitted from the luminophore is automatically manipulated by a computer. Thus, the Htun reference does not anticipate claim 73.

v. The Htun reference, even in view of the Carey and Agarwal references, does not teach each and every element in claim 77.

Claim 77 depends from claims 44, 45, and 46, and thereby includes the limitations thereof. As such, the Htun reference does not anticipate claim 77 for the same reasons it does not anticipate any one of claims 44-46. Additionally, claim 77 recites "selecting the one or more cells of the cell culture to be stable cells that are *stably transformed* with the nucleotide sequence coding for the hybrid polypeptide." Paragraph [0073] of the specification teaches that the cells can be stable transfectants, and paragraph [0100] provides an example of a CHO cell that is a stable transfectant that stably expresses the hybrid polypeptide. However, the Htun reference only teaches *transiently transformed* cells. Htun specifically states: "plasmid DNA was transiently introduced into 1471.1 cells" (page 4845, second column, last paragraph). Thus, Htun does not anticipate claim 77.

vi. The Htun reference, even in view of the Carey and Agarwal references, does not teach each and every element in claim 82.

Claim 82 depends from claim 80, which depends from claims 44, 45, and 46, and thereby includes the limitations thereof. As such, the Htun reference does not anticipate claim 82 for the same reasons it does not anticipate any one of claims 44-46. Additionally, claim 82 recites "implementing a spatial frequency method on the plurality of digital images, said spatial frequency method being selected from Fourier filtering, image cross-correlation, image

autocorrelation, object finding, object classification, color space manipulation for visualization, and combinations thereof." As such, the "spatial frequency method" must be selected from the methods listed in the claim. However, the Examiner did not point to any disclosure within Htun that teaches "Fourier filtering, image cross-correlation, image autocorrelation, object finding, object classification, [or] color space manipulation for visualization" (Office Action mailed 2/19/2009, page 5). Therefore, Htun cannot anticipate claim 82.

vii. Conclusion

For at least the foregoing reasons, Appellant respectfully submits that the Examiner has failed to establish that the Htun reference, even in view of the evidence of Carey and Agarwal, teaches each and every element of claims 44-52, 73, 77-80, and 82. Accordingly, the Examiner has not established a *prima facie* case of anticipation of the rejected claims 44-52, 73, 77-80, and 82 and the rejection should be overruled by the Board.

B. Issue 2: Whether claims 44-52, 73-80 and 82 are unpatentable under 35 U.S.C. § 103(a) over the Htun reference as evidenced by the Carey reference in view of the Agarwal reference, Sonenberg (US 5,874,231), and Dunlay (US 5,989,835).

Claims 44-52, 73-80 and 82 were rejected as being unpatentable under 35 U.S.C. § 103(a) over the Htun reference as evidenced by the Carey reference in view of the Agarwal reference, Sonenberg (US 5,874,231), and Dunlay (US 5,989,835). However, the Examiner has not established that the combination of references teach or suggest each and every element of the independent claims.

i. The combination of the Htun, Carey, Agarwal, Sonenberg and Dunley references does not teach or suggest each and every element in claims 44-45, 47-52, 73-80, and 82.

As discussed above, the Htun reference does not teach or suggest a "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component" and "a hybrid polypeptide comprising a luminophore

linked to the subunit." The other references in the Examiner's combination of references do not cure the deficiencies of Htun because none of the references teaches these limitations. The Examiner does not even acknowledge that these limitations may be missing from Htun. The Examiner only acknowledges that the limitations in claims 74-76 for "fixation of cells" and "well plates" are missing from Htun. The Examiner has therefore failed to establish a *prima facie* case of obviousness for claims 44-45, 47-52, 73-80, and 82.

Additionally, the Examiner's theory of obviousness relies on Htun teaching or suggesting that a hybrid polypeptide having a "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component" can be used in a "screening" method to determine whether a compound has a biological function or biological effect on the "subunit." As discussed above, since the biological function and biological effect on the GR protein was already well-known for dexamethasone, RU486, progesterone, and 17beta-estradiol prior to the work of the Htun reference, these compounds were not "screened" to determine whether they assert a biological function or biological effect on the GR protein in the work of the Htun reference. Moreover, none of the other references in the Examiner's combination of references teaches a "screening" to determine whether a compound has a biological function or biological effect on the "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component" as required by claims 44 and 45. Thus, the combination of references does not teach or suggest each and every element of 44-45, 47-52, 73-80, and 82, and a *prima facie* case of obviousness has not been established.

ii. The combination of the Htun, Carey, Agarwal, Sonenberg and Dunley references does not teach or suggest each and every element in claim 46.

The Examiner also has not established that the combination of references teach or suggest each and every element of claim 46. As recited above claim 46 recites that the "subunit" is "of a biologically active polypeptide" and the "subunit exhibits a biological activity of the polypeptide." None of the references in the combination teach or suggest a hybrid polypeptide that includes a "subunit of a biologically active polypeptide," let alone that such a hybrid polypeptide could be useful for a "screening." Since the combination of references (1) does not teach a hybrid polypeptide having a "subunit of a biologically active polypeptide" or (2) such a

hybrid polypeptide can be useful in "screening" as recited in the claims, the combination of references fails to teach or suggest each and every element of claim 46. Once again, the Examiner does not even acknowledge that these limitations may be missing from Htun. Thus, the combination of references does not teach or suggest each and every element of claim 46, and a *prima facie* case of obviousness has not been established.

iv. Conclusion

For at least the foregoing reasons, Appellant respectfully submits that the Examiner has failed to establish that the combination of references teaches or suggests each and every element of claims 44-52, 73-80, and 82. Accordingly, the Examiner has not established a *prima facie* case of obviousness of the rejected claims 44-52, 73-80 and 82, and the rejection should be overruled by the Board.

C. Issue 3: Whether claims 53 and 54 are unpatentable under 35 U.S.C. § 103(a) over the Htun reference, the Carey reference, the Agarwal reference, Sonenberg, and Dunlay, and further in view of the Cormack reference

Claims 53-54 were rejected as being unpatentable under 35 U.S.C. § 103(a) over the Htun reference as evidenced by the Carey reference in view of the Agarwal reference, Sonenberg (US 5,874,231), and Dunlay (US 5,989,835) as applied to claims 44-52, 73-80 and 82 above, and further in view of the Cormack reference. However, the Examiner has not established that the combination of references teach or suggest each and every element of the independent claims.

The Examiner's theory of obviousness for claims 53-54 relies on the Htun reference teaching or suggesting a hybrid polypeptide having a "subunit of a component" and/or a "subunit of a biologically active polypeptide" as recited in the claims. As discussed above, the Htun reference does not teach or suggest a "subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component," a "subunit of a biologically active polypeptide," or "culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a luminophore linked to the subunit under conditions permitting expression of the nucleotide sequence." The other references in the combination of references do not cure the deficiencies of Htun because none of

the references, let alone Cormack, teaches these limitations, and thereby, the combination of references still does not teach these limitations. The Examiner does not acknowledge that these limitations may be missing from Htun. In fact, the Examiner only asserts that the limitations in claims 53-54 for "GFP has the F64L mutation" are missing from Htun, Carey, Agarwal, Sonenberg, and Dunley, but provided by Cormack. Thus, the Examiner has therefore failed to establish a *prima facie* case of obviousness for claims 53-54.

For at least the foregoing reasons, Appellant respectfully submits that the Examiner has failed to establish that the combination of references teaches or suggests each and every element of claims 53-54. Accordingly, the Examiner has not established a *prima facie* case of obviousness of the rejected claims 53-54, and the rejection should be overruled by the Board.

D. Issue 4: Whether claim 48 fails to comply with the written description requirement under 35 U.S.C. §112, first paragraph

According to the Examiner, the teachings of the specification do not provide sufficient written description for screening a compound that is a "synthetic chemical compound" as recited in claim 48. Appellant respectfully disagrees. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention" (emphasis added). See, the MPEP 2163 (I); *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003). The Appellant clearly had possession of the concept of screening synthetic chemical compounds.

A compound is a synthetic chemical compound when the compound is prepared by chemical synthesis. The specification teaches that the compounds to be screened are a "compound or mixture of compounds prepared by organic synthesis" (paragraph [0118]), "chemical substances" (paragraphs [0012 and 0026]), and "chemical compounds" (paragraph [0124]). Taken together, these disclosures provide adequate written description for the screening of a "synthetic chemical compound." The reference to a "compound . . . prepared by organic synthesis" shows the inventor had possession of synthetic compounds, and the broad references to "chemical substances" and "chemical compounds" show the reference to "organic" synthesis is not limiting.

In view of the foregoing, the rejection of claim 48 under 35 U.S.C. §112, first paragraph, should be overruled by the Board.

CONCLUSIONS

Based on the foregoing, Appellant respectfully requests that the Examiner's rejections of claims 44-54, 73-80, and 82 be reversed based on the Examiner's failure to establish a proper *prima facie* case of anticipation and/or obviousness. For the foregoing reasons, Appellant respectfully requests that the Board reverse the Examiner's rejections and place the application in condition for immediate allowance.

The Commissioner is hereby authorized to charge payment of any of the following fees that may be applicable to this communication, or credit any overpayment, to Deposit Account No. 23-3187 (1) any filing fees required under 37 CFR § 1.16; (2) any patent application and reexamination processing fees under 37 CFR § 1.17; and/or (3) any post issuance fees under 37 CFR § 1.20. In addition, if any additional extension of time is required, which has not otherwise been requested, please consider this a petition therefore and charge any additional fees that may be required to Deposit Account No. 23-3178.

DATED this 30th day of September, 2009.

Respectfully submitted,

/Jonathan M. Benns, Reg. #53983/

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VIII. CLAIMS APPENDIX

Listing of Claims on Appeal:

Claims 1-43. (Cancelled).

44. (Previously Presented) A method for screening a library of compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component, comprising:

(a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a luminophore linked to the subunit under conditions permitting expression of the nucleotide sequence,

(b) incubating the one or more cells with at least one compound of the library of compounds,

(c) screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells, wherein translocation of the subunit in response to the at least one compound of the library of compounds determines that the at least one compound has a biological function or biological effect on the subunit, and

(d) measuring the light emitted from the luminophore in the incubated one or more cells and determining a variation with respect to the emitted light from said luminophore, such variation being indicative of the translocation of the subunit in said one or more cells and said translocation being indicative that said at least one compound of the library of compounds to be screened is biologically active with the component.

45. (Previously Presented) A method for screening a library of compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a component of an intracellular pathway affecting intracellular processes, which subunit exhibits a biological activity of the component, comprising:

(a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a luminophore linked to the subunit under conditions permitting expression of the nucleotide sequence,

(b) incubating the one or more cells with at least one compound of the library of compounds,

(c) screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells, wherein translocation of the subunit in response to the at least one compound of the library of compounds determines that the at least one compound has a biological function or biological effect on the subunit, and

(d) extracting quantitative information relating to the translocation of said subunit by determining a variation in spatially distributed light emitted from said luminophore, such variation being indicative of the translocation of the subunit in said one or more cells and said translocation being indicative that said at least one compound of the library of compounds to be screened is biologically active with the component.

46. (Previously Presented) A method for screening a library of compounds to detect a biologically active compound by detecting intracellular translocation of a subunit of a biologically active polypeptide affecting intracellular processes, which subunit exhibits a biological activity of the polypeptide, comprising:

(a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a luminophore linked to the subunit under conditions permitting expression of the nucleotide sequence,

(b) incubating the one or more cells with at least one compound of the library of compounds,

(c) screening the library of compounds to determine whether the at least one compound of the library of compounds has a biological function or biological effect on the subunit in the one or more cells, wherein translocation of the subunit in response to the at least one compound of the library of compounds determines that the at least one compound has a biological function or biological effect on the subunit,

(d) measuring the light emitted by the luminophore in the incubated one or more cells and determining a variation with respect to the emitted light, such result or variation being indicative of the translocation of the subunit in said one or more cells and said translocation being indicative that said at least one compound of the library of compounds to be screened is biologically active, and

(e) measuring the effect of said at least one compound of library of compounds on the inhibition/activation of biological activity of said subunit with the component.

47. (Previously Presented) A method according to claim 45, wherein the quantitative information relating to the translocation of the subunit is extracted from the recording or recordings according to a predetermined calibration.

48. (Previously Presented) A method according to claim 44, 45, or 46, wherein the compound to be screened for biological function or biological effect is a synthetic chemical compound.

49. (Previously Presented) A method according to claim 44, 45, or 46, wherein the compound is a drug whose affect on an intracellular pathway is to be determined.

50. (Previously Presented) A method according to claim 44, 45, or 46, wherein the intracellular pathway is an intracellular signaling pathway.

51. (Previously Presented) A method according to claim 44, 45, or 46, wherein the luminophore is a fluorophore.

52. (Previously Presented) A method according to claim 44, 45, or 46, wherein the luminophore is a Green Fluorescent Protein (GFP).

53. (Previously Presented) A method according to claim 52, wherein the GFP has the F64L mutation.

54. (Previously Presented) A method according to claim 52, wherein the GFP is a GFP variant selected from the group of consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.

55.-72. (Cancelled)

73. (Previously Presented) A method according to claim 44, 45, or 46, wherein the light emitted from the luminophore is obtained by automated image acquisition.

74. (Previously Presented) A method according to claim 44, 45, or 46, wherein the cells are fixed prior to light emitted from the luminophore being measured or used in determining the variation.

75. (Previously Presented) A method according to claim 44, 45, or 46, wherein the cells are cultured and incubating with the at least one compound of the library of compounds in a well plate.

76. (Previously Presented) A method according to claim 44, 45, or 46, further comprising fixing the one or more cells of the cell culture.

77. (Previously Presented) A method according to claim 44, 45, or 46, further comprising selecting the one or more cells of the cell culture to be stable cells that are stably transformed with the nucleotide sequence coding for the hybrid polypeptide.

78. (Previously Presented) A method according to claim 44, 45, or 46, wherein the component is a protein.

79. (Previously Presented) A method as in claim 78, wherein said at least a subunit of the component is substantially the entire protein.

80. (Previously Presented) A method as in claim 44, 45, or 46, further comprising recording a plurality of digital images of the light emitted from the luminophore.

81. (Withdrawn) A method as in claim 80, further comprising implementing a digital filtering method on the plurality of digital images, said filtering method being selected from the group consisting of smoothing, sharpening, edge detection, and combinations thereof.

82. (Previously Presented) A method as in claim 80, further comprising implementing a spatial frequency method on the plurality of digital images, said spatial frequency method being selected from Fourier filtering, image cross-correlation, image autocorrelation, object finding, object classification, color space manipulation for visualization, and combinations thereof.

IX. EVIDENCE APPENDIX

FILED ELECTRONICALLY

PATENT APPLICATION
Docket No. 16778.5a.1.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In application of:		
	Ole Thastrup et al.	
		Art Unit
Serial No.	10/072,036	1633
Confirmation No.	3912	
For:	A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE	
Filing Date:	February 5, 2002	
Examiner:	M.D. Burkhart	
Customer No.	022913	

DECLARATION OF CHRIS M. IRELAND, PH.D.

UNDER 37 C.F.R. § 1.132

Mail Stop AMENDMENT
Commissioner for Patents P.O.
Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Chris M. Ireland, Ph.D., hereby declare as follows:

1. I am personally knowledgeable of the facts stated herein.

2. I am a professor and chairman of the Department of Medicinal Chemistry in the College of Pharmacy at the University of Utah, Salt Lake City, Utah. I have significant experience in preparing compounds and screening compounds for biological activity (*see* Appendix A: Curriculum Vitae of Chris M. Ireland). Additionally, I am knowledgeable in the field of developing and validating high throughput screening (HTS) assays for biological activity and drug development, and also knowledgeable in the field of formatting and processing of chemical diversity libraries for use in HTS assays. I am therefore knowledgeable in the field preparing and screening compounds for biological activity, such as disclosed and claimed in the U.S. Patent Application Serial No.10/072,036 ("Subject Application"), which is currently under examination.

3. I have reviewed and understand the Subject Application and the *Carey* reference cited by the Examiner in the Office Action of October 20, 2006.

4. I am not an inventor of the subject matter disclosed and claimed in the Subject Application.

5. I am not currently employed by and have never been employed or associated with Fisher BioImage ApS or Thermo Fisher Scientific.

6. I do not have a personal interest in the Subject Application.

7. A dictionary definition of "library" reads as follows: "[a] place in which literary and artistic materials, such as books, periodicals, newspapers, pamphlets, prints, records, and tapes, are kept for reading, reference, or lending"; "[a] collection of such materials, especially when systematically arranged"; "[a] room in a private home for such a collection"; "[a]n institution or foundation maintaining such a collection"; "[a] commercial establishment that lends books for a fee"; "[a] series or set of books issued by a publisher"; "[a] collection of recorded data or tapes arranged for ease of use"; "[a] set of things similar to a library in appearance, function, or organization: *a library of computer programs*"; and "*Genetics* A collection of cloned DNA sequences whose location and identity can be established by mapping the genome of a particular organism." (See, *The American Heritage® Dictionary of the English Language, Fourth Edition.* Houghton Mifflin Company, 2004. 21 Feb. 2007. <Dictionary.com http://dictionary.reference.com/browse/library> .)

8. A dictionary definition of "compounds" with respect to the field of chemistry reads as follows: "[a] pure, macroscopically homogeneous substance consisting of atoms or ions of two or more different elements in definite proportions that cannot be separated by physical means. A compound usually has properties unlike those of its constituent elements." (See, *The American Heritage ® Dictionary of the English Language, Fourth Edition.* Houghton Mifflin Company, 2004. 23 Feb. 2007. <Dictionary.com http://dictionary.reference.com/browse/ compound>.)

9. The ordinary meaning of a "library of compounds," as evidenced by the aforementioned dictionary definitions, is a collection of compounds that are either pure or present at a known concentration, and such compounds of the library of compounds are arranged for ease of use. Additionally, the plain meaning of a "library of compounds" is similar to a standard book library in appearance, function, or organization.

10. As used in the Subject Application, a "library of compounds" is a term of art that is well known to those of ordinary skill in the art of screening compounds. A skilled artisan in the art of screening compounds would understand a "library of compounds" to be a collection of compounds that

are either pure or present at a known concentration, and arranged so that each compound can be selected from the collection of compounds for use in an experiment either alone or in combination with other compounds of the library. Also, a skilled artisan would understand that a library of compounds is a collection of compounds assembled for the purpose of testing the compounds to determine suitability for a particular purpose, or to detect wanted or unwanted attributes of the compounds. Additionally, a skilled artisan would understand that a "library of compounds" has a function similar to a standard book library in that each compound of the collection of compounds is individually retained within a container such that a single compound of the collection of compounds can be individually selected for use similar to how a single book can be selected in a standard book library. The compounds can be individually retained in the container in a pure state or in a specific, known concentration in a specific solvent that is compatible with the environment in which the compound will be used, wherein the container is substantially devoid of any contaminating compounds or substances. Furthermore, a skilled artisan would understand that more than one compound of a "library of compounds" can be selected as a group for use similarly to how a group of books can be selected in a standard book library.

11. A dictionary definition of "screening" reads as follows: "[t]o examine (a job applicant, for example) systematically in order to determine suitability"; "[t]o test or evaluate (a student) to determine placement in an educational system or to identify specific learning needs"; "[t]o test or examine for the presence of disease or infection: *screen blood; screen a patient*"; "[t]o subject to genetic screening"; and "[a] systematic examination or assessment, done especially to detect an unwanted substance or attribute. (See, *The American Heritage® Dictionary of the English Language, Fourth Edition*. Houghton Mifflin Company, 2004. 23 Feb. 2007. <Dictionary. com http://dictionary.reference. comlbrowse/ screening>.)

12. The ordinary meaning of "screening a library of compounds," as evidenced by the aforementioned dictionary definitions, is a process to systematically examine, test, or evaluate the compounds or a combination of compounds of a library of compounds to determine suitability for a particular purpose, or detect wanted or unwanted attributes of the compound.

13. As used in the Subject Application, "screening a library of compounds" is a term of art for an experimental process that is well known to those of ordinary skill in the art of screening compounds. A skilled artisan in the art of screening compounds would understand "screening a library of compounds" to be a process to systematically examine, test, or evaluate the compounds of the library of compounds in order to determine suitability for a particular purpose, or to detect wanted or

unwanted attributes of the compounds. Additionally, a skilled artisan in the art of screening compounds would understand that "screening a library of compounds" would include a process to systematically examine, test, or evaluate whether or not a known concentration of a compound or a combination of compounds of the library of compounds is biologically active, and so that the biological activity can be correctly attributed to a known concentration of the compound. Furthermore, such "screening a library of compounds" inherently includes comparing a compound or a combination of compounds of the library of compounds to a control so that the presence or absence of any biological activity is correctly attributed to the compound or combination of compounds.

14. The specification of the Subject Application (PG-PUB 2003/0082564) discloses a "library of compounds" at the following paragraphs: [0027] and [0193]. Additionally, the specification of the Subject Application (PG-PUB 2003/0082564) discloses a "screening" at paragraphs [0001], [0013], [0027], [0036], [0058-0063], and [0126-0141]. The Examples and Figures describe protocols and illustrate results for such a screening. Thus, the Subject Application discloses "screening a library of components."

15. The *Carey* reference does not disclose a "library of compounds" or a group of compounds that could be construed as a "library of compounds" because there is no reference to a collection of compounds that are each either pure or present at a known concentration, and that are assembled for the purpose of testing the compounds to determine suitability for a particular purpose, or to detect wanted or unwanted attributes of the compounds.

16. A skilled artisan would not consider "any and all substances [or compounds] mentioned in the Materials and Methods section on pages 986-987" in the *Carey* reference to be a library of compounds. In part, this is because the substances of *Carey* are not described to have each compound of the substance to be individually retained within a container at a known concentration such that a single compound of the substance can be individually selected. Additionally, the Materials and Methods section of *Carey* does not teach or suggest the compounds recited therein are a "library of compounds" that are assembled for the purpose of testing the compounds to determine suitability for a particular purpose, or to detect wanted or unwanted attributes of the compounds.

17. A skilled artisan would not consider dexamethasone, phenol red, serum, and charcoal-stripped serum to be a library of compounds because only dexamethasone could be construed to be a compound that is either pure or present at a known concentration. Also, *Carey* does not teach or suggest that phenol red is available for being selected in the absence of cell culture media, and thereby phenol red is not taught or suggested to be present in a pure state or in a specific, known concentration

in a specific solvent that is compatible with the environment in which the compound will be used, wherein the solvent is substantially devoid of any contaminating compounds or substances because the other compounds contained in media would be considered to be contaminants. Additionally, neither serum nor charcoal-stripped serum is a pure compound, and the compounds contained therein are not all present at known concentrations.

18. A skilled artisan would not consider the compounds contained in serum or charcoal-stripped serum to be a library of compounds because the compounds contained therein are not pure and are not all present at known concentrations because serum contains many compounds at unknown concentrations. Also, the compounds of serum are not a collection of compounds that are individually retained within a container such that a single compound can be individually selected.

19. The *Carey* reference does not disclose a method of "screening a library of compounds," or reference any experiment *(e.g.,* experiments conducted with dexamethasone, phenol red, serum, and/or charcoal-stripped serum) that a skilled artisan would construe as "screening a library of compounds" because a "library of compounds" is not taught or suggested as discussed above. Additionally, only dexamethasone could be construed to be in a pure state or at a known concentration that is included in a process to be systematically tested to determine suitability for a particular purpose, or to detect wanted or unwanted attributes, and testing dexamethasone alone does not constitute "screening a library of compounds."

20. I declare further that all statements made herein of my own knowledge are true and that all statements are made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 20th day of March, 2007.

CHRIS M. IRELAND, Ph.D

X. RELATED PROCEEDINGS APPENDIX

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination
	10/072,036	THASTRUP ET AL
	Joseph T. Woitach	Art Unit 1633

Document Code - AP.PRE.DEC

Notice of Panel Decision from Pre-Appeal Brief Review

This is in response to the Pre-Appeal Brief Request for Review filed 8/29/2007.

1. ☐ **Improper Request** – The Request is improper and a conference will not be held for the following reason(s):

☐ The Notice of Appeal has not been filed concurrent with the Pre-Appeal Brief Request.
☐ The request does not include reasons why a review is appropriate.
☐ A proposed amendment is included with the Pre-Appeal Brief request.
☐ Other:

The time period for filing a response continues to run from the receipt date of the Notice of Appeal or from the mail date of the last Office communication, if no Notice of Appeal has been received.

2. ☐ **Proceed to Board of Patent Appeals and Interferences** – A Pre-Appeal Brief conference has been held. The application remains under appeal because there is at least one actual issue for appeal. Applicant is required to submit an appeal brief in accordance with 37 CFR 41.37. The time period for filing an appeal brief will be reset to be one month from mailing this decision, or the balance of the two-month time period running from the receipt of the notice of appeal, whichever is greater. Further, the time period for filing of the appeal brief is extendible under 37 CFR 1.136 based upon the mail date of this decision or the receipt date of the notice of appeal, as applicable.

☐ The panel has determined the status of the claim(s) is as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: _____.
Claim(s) withdrawn from consideration: _____.

3. ☐ **Allowable application** – A conference has been held. The rejection is withdrawn and a Notice of Allowance will be mailed. Prosecution on the merits remains closed. No further action is required by applicant at this time.

4. ☒ **Reopen Prosecution** – A conference has been held. The rejection is withdrawn and a new Office action will be mailed. No further action is required by applicant at this time.

All participants:

(1) *Joseph T. Woitach*. (3) *Robert Wax*.

(2) *Michael Burkhart*. (4)_____.

Joe Woitach AU1633

U.S. Patent and Trademark Office

Part of Paper No: 20070924